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EDITORIAL

Resisting resistance to cancer immunotherapy

Cancer immunosurveillance is the process of an intact immune system detecting and eradicating neoplastic cells. Immunoediting is a process by which a tumor cell overcomes the process of tumor elimination, going through a period of equilibrium with the immune system and eventually leading to tumor escape.[1] Research conducted during the past three decades has exposed a myriad of pathways exploited by human malignancies to evade immunological destruction. Most notably, inhibitory immune checkpoints such as CTLA-4 and PD-1/PD-L1, which normally maintain peripheral tolerance by disabling the activation and effector functions of autoreactive T-cells, have been found to be co-opted in a majority of common cancer types. Establishing the clinical efficacy of monoclonal antibodies that neutralize these pathways has represented a significant step forward in incorporating immunotherapy into the anti-cancer armamentarium.

Unfortunately, a well-known contrivance of neoplasia is to continuously evolve and become resistant to anticancer therapies. Observations of acquired resistance to immune checkpoint blockade occurring in a substantial proportion of patients enrolled in clinical trials – often months or years after an initial meaningful response – should come as a sobering reminder of the need to continuously identify resistance pathways to overcome.[2] As immunotherapy is incorporated into routine clinical practice, an increase in the number of reported cases of relapse is to be expected. Ipso facto, it is imperative to consider combination or sequential strategies to overcome such resistance. In a recent review article by Syn *et al.,* the complexity of mechanisms that abet the formation of so-called "immunoresistant niches" have been detailed.[2] The authors propose a conceptual framework encompassing 10 major hallmarks of cancer immunoresistance (numbered in parentheses in the succeeding paragraphs). It appears that mechanisms of acquired resistance parallel those that underpin intrinsic resistance to immunotherapy, although subtle contextual nuances in the basis of the two phenotypes may be appreciated.

The first overarching mechanism proposed is that of a defective tumor immunorecognition system, which subsumes the following concepts: (i) disabled antigen presentation, (ii) limited neoantigen repertoire (which itself could be a consequence of immunoediting), and (iii) insufficient diversity and abundance of CD8 T-cells. Indeed, these three ideas correspond to the individual steps of tumor antigen presentation and priming of the adaptive immune system, and the notion that defective tumor immunorecognition restrains both natural and therapy-elicited immunosurveillance is now well-recognized.[3] Current clinical research focuses on the combination of immune checkpoint inhibitors and (DNA-damaging) cytotoxic chemotherapeutic agents. It may seem counterintuitive to employ cytotoxic agents in a strategy aimed at enhancing T-cell activation and clonal expansion, as it could potentially attenuate immune cells and responses required for antitumor immunity. However, pre-clinical studies have demonstrated that DNA-damaging agents, in addition to their direct cytotoxic effects, have the added benefit of promoting immunogenicity. Enhanced immunogenicity may be achieved through two mechanisms – directly promoting antigenicity of the tumor through the disruption of DNA, and indirectly lifting immunosuppression within the tumor microenvironment.[4] Blank *et al.* have described a spectrum of tumor immunogenicity – "inflammatory" tumors tend to be responsive to checkpoint inhibition, limiting combination therapy usage to tumors that have acquired resistance, whereas "immune desert"-type tumors probably require the complementary effect of combination therapy to achieve significant clinical effect.[5]

Nevertheless, cancer cells have a range of adaptive programs to limit DNA damage induced by genotoxic agents, which are linked to innate and adaptive immunity. Inhibiting these DNA-repair mechanisms may possibly enhance tumor foreignness,[4] but may come at the price of dampening the effects of immune checkpoint inhibitors. Combination therapy of anti-DNA-repair agents and immune checkpoint inhibitors may be promising, because of the potential for reducing toxicity associated with the latter.[4]

A second overarching mechanism proposed by Syn *et al.* relates to the tumor microenvironment and neovasculature, and encompasses the following three concepts: (iv) the immune contexture (i.e. extent of T-cell infiltration and reactivity), (v) deregulation of immunometabolism, and (vi) angiogenesis.[2] Indeed, cancer cells interact within a dynamic and stochastic microenvironment with heterotypic cell types. An abundance of literature has emerged in recent years describing how these ostensibly "normal" cells in the tumor microenvironment contribute to spatially-limited "immunoresistant niches." For instance, proangiogenic VEGF signaling features in tumors that are resistant to immunotherapy, and the tumor neovasculature may play a role in selectively culling assailing CD8 T-cells while posing a formidable physical barrier to their extravasation. Crucially, vascular normalization with anti-angiogenic

therapies has shown promise in improving lymphocyte trafficking across the endothelium and reversing immunotherapy resistance. Emerging evidence also suggests that derangements of T-cell immunometabolism – particularly as a result of hypoxia, high concentrations of tumor-derived lactic acid, and scarcity of glucose and amino acids in the tumor microenvironment – can encumber the activation and effector functions of antitumor T-lymphocytes. Identifying biomarkers pertaining to the tumor microenvironment to predict response or resistance to immunotherapy thus represents a necessary, albeit challenging, logical next step.

Aside from the contributions of defective tumor immunorecognition, the tumor microenvironment, and neovasculature to immunotherapeutic resistance, a further four resistance mechanisms were enumerated: (vii) insensitivity to immune effector molecules (e.g. IFN-γ and FasL), (viii) tumor plasticity and stemness, (ix) the enteric microbiome, and (x) co-option of alternative immune checkpoints. The role of epithelial-to-mesenchymal transition (EMT) in fostering tumor plasticity is less well known and warrants further discussion. Studies conducted in the past have promulgated the notion that inflammation-driven tumor plasticity, which may occur through EMT programs, is partly responsible for mediating therapeutic resistance to cytotoxic drugs, targeted therapies, and radiation therapy. Thus, recent findings that inflammatory immune infiltrates may also paradoxically engender resistance to adoptive T-cell transfer or checkpoint blockade immunotherapy through EMT programs.[2] In addition, the role of gut microbiota in dictating a response to immunotherapy has become the subject of intensive research in the past few months, with multiple studies reporting correlations between various microbial constellations with immunotherapy efficacy. Unfortunately, these associations have not been consistent across studies, and various points of conjecture exist as to how gut bacteria may modify immunotherapy response and resistance. Until mechanisms of how enteric bacteria modulate the adjuvanticity of immune response are fully elucidated, it seems less likely that rational approaches can be devised to harness the enteric microbiome to salvage resistance to cancer immunotherapy.

Enumerating the multifactorial mechanisms through which resistance to immune checkpoint blockade occurs may only be half of the battle. We have discussed the importance of having frameworks to understand the mechanisms at play in developing resistant tumors, and having biomarkers to predict the likelihood and gauge the extent of response, if any. Identifying these functional barriers to immunotherapy is critical to protract the efficacy of immunotherapy, or enable immune checkpoint blockage on previously intractable malignancies. It is also important to consider other current issues and future perspectives in the management of patients treated with immunotherapy. The wide range of adverse effects documented with immunotherapy, from endocrinopathies to gastrointestinal toxicities and autoimmune inflammatory conditions, hints at possible pharmacogenomic underpinnings and represents a unique and emerging challenge. For future research, it is important that clinical development of immune checkpoint blockade continues to embrace parallel developments in genomics, epigenomics, and precision medicine. Like targeted therapies, we envisage that optimal use of cancer immunotherapy will hinge on the identification of mechanistic biomarkers of response and resistance, and this in turn underscores the importance of conceptual frameworks for conceiving the cancer-immunity interplay, and to guide research agendas over the next decade.

Disclosure

No authors report any conflict of interest.

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References

1 Dunn GP, Bruce AT, Ikeda H, Old LJ, Schreiber RD. Cancer immunoediting: From immunosurveillance to tumor escape. *Nat Immunol* 2002; **3**: 991–8.

2 Syn NL, Teng MWL, Mok TSK, Soo RA. De-novo and acquired resistance to immune checkpoint targeting. *Lancet Oncol* 2017; **18** (12): e731–41.

3 Syn N, Tay D, Mohd Omar MF *et al.* Mutational features associated with immunoreactivity in non-small cell lung cancer. *J Thorac Oncol* 2017; **12** (1 Suppl): S821.

4 Brown JS, Sundar R, Lopez J. Combining DNA damaging therapeutics with immunotherapy: More haste, less speed. *Br J Cancer* 2018; **3**: 312–24.

5 Blank CU, Haanen JB, Ribas A, Schumacher TN. The "cancer immunogram.". *Science* 2016; **352**: 658–60.

